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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,657	02/19/1999	PETER RUHDAL JENSEN	55411.000002	1335

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HUNTON & WILLIAMS
INTELLECTUAL PROPERTY DEPARTMENT
1900 K STREET, N.W.
SUITE 1200
WASHINGTON, DC 20006-1109

EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	**PAPER NUMBER**
1636	36

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/242,657	JENSEN ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,13-18,21-23,25 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *16 and 22* is/are allowed.

6)☒ Claim(s) *1-4,6-11,13-15,17,18,21,23,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a response, filed 9/28/03 as Paper No. 34, in which several claims were cancelled (claims 5, 12, 19 and 20) and in which several claims were amended (claims 1, 6, 13, 15-18, 21-23, 25 and 27). Claims 1-4, 6-11, 13-18, 21-23, 25 and 27 are pending in the instant application.

Any rejection of record in the instant application not addressed in this action is withdrawn. This action is FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11, 13-15, 18, 23, 25 & 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in Paper No. 31, mailed 3/11/03 and repeated below.**

Claims 1-4, 6-11, 13-15, 23, 25 & 27 are drawn to a set of promoters suitable for optimizing expression of a gene in a selected organism or group of organisms wherein the set of promoters comprise at least two consensus sequences where at least half of the consensus sequences are kept constant across the promoter set. The set of promoters must cover "a range of activities" of "a" gene in small steps, each step changing the promoter activity by 50-100%. For

prokaryotic promoters, the conserved sequences can be selected from the group consisting of TATAAT, TTGACA and an activator binding sequence upstream of the TATAAT sequence. For eukaryotic organisms, the at least two consensus sequences being selected from the group consisting of a TATA-box and a UAS upstream of the TATA-box, and where the promoter set further has a randomized spacer sequence between the two consensus sequences or flanking at least one of the conserved sequences. Claims 18-20 are drawn towards methods of using subsets of promoter sequences obtained from the first set of promoter sequences to drive expression of a desired gene in an organism or groups of organisms, or to control the flux of a metabolite in the desired organism or group of organisms.

The rejected claims thus comprise a set of promoters that can be derived from any source to drive expression of any gene in any organism (e.g. humans, archaebacteria, etc.) or any combination of organisms (e.g. meeting the claim's functional limitations in both humans and fish, or humans and S. aureus). The upstream activator sequences can be literally of any type. The set of promoters must drive expression of the operably linked gene to a particular range of any possible range of activities. Functionally, the set of promoters must cover the range of expression in steps of 50-100%. Thus, the rejected claims encompass an incredibly enormous genus of promoter sets that must meet very specific functional limitations (i.e. expression of a gene in a particular organism, or combination of organisms, in steps of 50-100% change in activity levels). For example, the limitation of covering the range of expression in steps of 50-100% greatly increases the description problems for the rejected claims. If one stipulates a single range of promoter activity for the claimed promoter set as from 1-100 units/hour, one can cover the range in steps of ~25 units/hour, ~10 units/hour, ~2 units/hour, etc. Thus, for every

range of promoter activity, one can traverse the range in steps of 50-100% changes in activity in many different ways. Each of these different ways of traversing a given range of activity is likely to involve a series of different promoter constructs, each set possessing a different collection of promoters having different changes in the promoter sequence/structure. Given that the range of activities encompassed by the instant claims is any that is biologically possible, and that the claims encompass regulating the expression of literally any gene in any single organism, or combination of different organisms, the genus of promoter sets encompassed by the rejected claims is so broad as to be incalculable.

The instant specification describes consensus promoter sequences observed in a few different prokaryotic or eukaryotic microorganisms (e.g. *L. lactis, E. coli, S. cerevisiae*) and describes experiments wherein a range of different promoter activities in different microorganisms is obtained. There is no description in the specification as originally filed of any promoter set that would meet the claim limitations in any particular multi-cellular organism (e.g. humans). While the range of activity obtained in some cases is impressive (e.g. Example1 and Figure 1), it is not clear from reading the examples and the legends to the figures that the promoter sets described necessarily meet the claim limitations (i.e. wherein half of at least two consensus sequences in at least two promoters in the library of promoters are conserved and wherein the at least two promoters only differ in activity by 50-100%). For example, the activities shown in Figures 1 & 3 are given on a logarithmic plot with no clear indicate that any two "adjacent" promoters necessarily meet the structural/functional limitations of the claim (e.g. on the logarithmic scale shown in these figures a difference in activity for "adjacent" promoters having 2-fold or 100% difference in activity cannot be clearly determined).

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of expression of a single gene in a single microorganism over, at best, a few possible ranges wherein the promoters within the set meet the functional limitations of the claims (e.g. a few possible subsets within the broader range of activities shown in Figure 1). The results described are not necessarily predictive of promoter set structure for expression of different genes in the same organism (e.g. differences in transcription rates, transcript stability, etc.) or for the expression pattern of a given promoter set in a different organism. This is especially true for combinations of different organisms. For example, while certain promoter elements may be somewhat conserved across species lines (e.g. a TATA box), upstream activator binding sites of the invention would necessarily be expected to vary across species lines (e.g. human and shrimp), making it impossible for one to extrapolate from the few promoters described herein those promoter sets that would necessarily meet the functional/structural characteristics of the rejected claims. The prior art also does not appear to provide a reliable basis for one of skill in the art to envision promoter sets that will necessarily meet the structural/functional limitations of the rejected claims for a given gene in an organism or groups of organisms.

There remains no structural/functional basis for one of skill in the art to envision those promoter sets that 1) retain the conserved sequences and 2) satisfy the functional limitations of the claim with regard to step-wise increments in promoter activity amongst the members of the promoter set for the incredibly broad genus of such promoter sets encompassed by the rejected claims (i.e. literally any combination of activity range, gene and organism, or combination of organisms). Therefore, one of skill in the art would not have been able to envision a

representative number of specific promoter sets to describe the broad genus of promoter sets encompassed by the rejected claims. One of skill in the art would thus have reasonably concluded applicants were not in possession of the claimed invention for claims 1-15, 18-21, 23, 25 and 27.

Response to Arguments/112 1st Written Description

Applicant's arguments filed in Paper No. 34 have been fully considered but they are not persuasive. The response essentially argues: 1) applicants have amended the claims to limit the scope to microorganisms, 2) the examiner's appreciation of the full scope of the claims is evidence that the invention has been described in such a way that the skilled artisan would recognize applicants were in possession of the claimed invention, 3) the promoters of the invention are structurally and functionally characterized, 4) the specification has provided sufficient identifying structural and functional characteristics to show applicants were in possession of the claimed invention, 5) the specification does disclose a representative number of specific embodiments (e.g. Examples 1-2, Example 7), 6) the specification provides methodologies for determining/constructing such promoters, and 7) to deny applicants patent on the basis that their invention may be applied to a large number of desired microorganisms is tantamount to denying them a patent because their invention is too effective and useful.

While the amendment of the claims to limit the host organisms embraced by the rejected claims to microorganisms is appreciated, it does not go far enough in terms of limiting the scope of the organisms embraced by the rejected claims. The claims still encompass an enormous genus of bacteria, fungi, thermophiles, protests, etc. The observation that the examiner has an appreciation for the full scope of the invention is gratefully acknowledged, but is irrelevant with

regard to the grounds for making the written description rejection. Those grounds remain an insufficient basis for one of skill in the art to envision those promoter sets encompassed by the rejected claims. For example, applicants' arguments have not addressed the issues of the many different expression ranges embraced by the claims for expression of a single gene in a single organism, or the issue of how different genes are expressed based upon other factors (e.g. differences in RNA structure, etc.). The specification has provided no guidance with regard to what the promoter sets would look like in any number of different microorganisms and still satisfy the functional limitations of the claims (e.g. in protozoa or in thermophyllic bacteria, etc.). It is not even clear that the few examples given in the specification actually meet the functional limitations of the claims for any given gene. Even if one were to concede that the description provided for E. coli, yeast and lactobacteria in the specification does meet the functional limitation of the claims, this cannot be considered sufficient to describe the broadly claimed genus of literally any microorganism expressing literally any gene. Finally, the examiner never made the rejection in terms of applicants' invention being too effective or too useful. In fact, the whole point of the rejection is that one of skill in the art would not have recognized that applicants' were in possession of the full, broadly claimed scope of the invention.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments featuring promoter sets that regulate expression of a desired gene in an organism, does not reasonably provide enablement for any embodiment wherein the flux of a cellular metabolite is controlled. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and practice the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in Paper No. 31, mailed 3/11/03 and repeated below.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The invention is complex, involving the generation of promoter sets that are functional in an organism to regulate expression a given gene so as to control the flux within the organism of a cellular metabolite. In order to construct promoter sets to use in the claimed method one must understand the effect of the desired gene on cellular metabolism for the desired host cell of a particular metabolite. This effect is greatly increased when the cell is located within a higher-level or multi-cellular organism where systemic physiology must be taken into account.

Breadth of the claims: The great breadth of the claims only exacerbate the complexity of the invention. The claims encompass promoter sets that are to be functional in any organism (e.g. human, rice, mouse, alfalfa, sea slug, etc.), microbial or multi-cellular, for the expression of any gene from any source over any given range of promoter activity. The limitation where a promoter of the invention is used to control the "flux" of any metabolite in an organism of any type greatly exacerbates the complexity of the invention, requiring, at a minimum, knowledge of

the metabolic physiology at the cellular level of literally any metabolite in any host organism, or combination of organisms.

Guidance of the specification/Existence of Working Examples: The teachings of the instant specification are directed exclusively towards microbial promoters and upstream regulatory elements (e.g. in *S. cerevisiae* or *L. lactis*). There are no teachings, for example, for constructing promoter sets in multi-cellular organisms that meet the functional limitation of step-wise increments of promoter activity of 50-100% within that multi-cellular organism, much less in combinations of such higher organisms. There is no teaching of constructing promoter sets for the regulation of the cellular flux of a particular metabolite in any organism, much less a multi-cellular organism where systemic physiology will play a role in the flux of the metabolite in the organism. There are no working examples directed to controlling the "flux" of any particular metabolite in any particular organism.

State of the art/ Predictability of the art: The art of metabolic engineering is not predictable. In a review of the art concerning the metabolic engineering, Bailey teaches that there are a large number of variables that must be considered in making recombinant microorganism that produce a desired metabolite in a desired manner (Science, Vol. 252, pages 1668-1675; see the entire reference). These factors include, among others, how the gene is expressed in the cell, protein stability for the expressed gene product, and the global effects of the expression of the protein on the host cell (e.g. page 1674, final paragraph). For example, expression of even low concentrations of unnatural proteins can activate stress response, influencing many cell functions. Bailey concludes, "Although some of the experimental and mathematical tools required for rational metabolic engineering are available, complex cellular

responses to genetic perturbations can complicate predictive design." (Abstract). The state of the art for practicing the claimed invention in multicellular organisms (e.g. humans, rice, etc.) would necessarily be even more unpredictable in that systemic physiology involving multiple tissue types would need be taken into account in practicing the invention in a predictable manner.

The amount of experimentation necessary: Given the factors outlined above, and the unpredictability of the art, it would have required undue trial-and-error experimentation of an unpredictable nature for one skill in the art to practice the claimed methods.

Response to Arguments/112 1st Written Description

Applicant's arguments filed in Paper No. 34 have been fully considered but they are not persuasive. The response essentially argues: 1) identification of conserved sequences is well within the skill of the art, 2) selection of promoter sequences that increase expression of a given gene in a host cell by steps of 50-100% is well within the skill of the art, 3) the invention lies in the realization that randomly changing the promoter sequence of spacer sequences, promoter strength can be varied to provide a promoter set having a wide range of activities and the expression of a given gene in a selected microorganism can be optimized by using an optimized promoter, and 4) a person skilled in the art would be able to construct and use such a set of promoters covering the range of activities as recited in the rejected claim.

The arguments presented in Paper No. 34 have missed the point of the rejection. The rejection was not made on the basis of being able to construct a promoter set that comprises promoters expressing a given gene at steps of 50-100% in a given microorganism. The point of the rejection is that the method, as directed to regulation of the flux of a cellular metabolite is not enabled by the instant specification. As none of the arguments are on point, the rejection stands.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections.**

Claim 17 is vague and indefinite in that it does not make clear that the plurality of promoter sequences that drives expression of the gene at steps of 50-100% does so in the same microorganism as in which the conserved sequences were identified. Thus, there is no clear antecedent basis for the host cell in the limitation of covering a range of promoter activities. It would be remedial to amend the claim language to clearly indicate that the microorganism of claim 17 is the same used in claim 16.

Claim 21 is vague and indefinite in that there is no clear and positive prior antecedent basis for the term "the pathway" in the preamble of the claim.

Conclusion

Claims 1-4, 6-11, 13-18, 21-23, 25 and 27 are pending in the instant application. Claims 1-4, 6-11, 13-15, 17-18, 21, 23, 25 & 27 are rejected. Claims 16 and 22 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

GERRY LEFFERS
PRIMARY EXAMINER

Gerald G Leffers Jr., PhD
Examiner
Art Unit 1636

Ggl